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(54) Title: LABORATORY IN A DISK

(57) Abstract

An apparatus is described that includes an optical disk, adapted to be read by an optical reader, comprising a first sector having substantially self-contained assay means for localizing an analyte suspected of being in a sample to at least one, predetermined location in the first sector and a second sector containing control means for conducting the assay and analyte location information, with respect to one or more analytes suspected of being in a sample, accessible to the reader, wherein the presence or absence of the analyte at said location is determinable by the reader using the control means and the location information. Depending on the nature of the assay, the disk will include fluid storage means, fluid transfer means, such as one or more capillary ducts, valves, batteries, dialyzers, columns, filters, sources of electric fields, wires or other electrical conductive means such as metallic surface deposits and the like.

LABORATORY IN A DISK

FIELD OF THE INVENTION

This invention relates generally to diagnostic assays and methodology therefor. In particular, it relates to diagnostic assay components configured on a compact optical disk and methodology for the use thereof.

BACKGROUND

There is an enormous need to make clinical assays faster, cheaper and simpler to perform. Ideally patients should be able to test themselves, if so desired. One way towards this goal has been through miniaturization and integration of various assay operations. Currently, a number of bio-chip assays (so-called because some are built using silicon chip photolithography techniques) are commercially available or under development. All of these approaches require a reading machine and a computer.

Disk-shaped cassettes used for clinical assays in conjunction with UV/Vis spectrometry are also commercially available. U.S. Patent No. 5,122,284 describes a centrifugal rotor that contains a number of interconnected fluid chambers connected to a plurality of cuvettes. The rotor is adapted to be utilized with a conventional laboratory centrifuge, and is formed of materials that allow photometric detection of the results of assays that have been carried out in the reaction cuvettes. A large number of rotor configurations and related apparatus for the same or similar types of analysis have been described. See for example U.S. Patents 5,472,603; 5,173,193; 5,061,381; 5,304,348; 5, 518,930; 5,457,053; 5,409,665; 5,160,702; 5,173,262; 5,409,665; 5,591,643; 5,186,844; 5,122,284; 5,242,606; and patents listed therein. Lyophilized reagents for use in such systems are described in U.S. Patent 5,413,732.

The principles of a centrifugal analyzer have been adapted into a disk that can be used in a CD-drive like instrument (Mian, et al., WO 97/21090 Application). Mian

SUMMARY OF THE INVENTION

In one aspect, the invention is directed to an optical disk, adapted to be read by an optical reader, comprising a first sector having a substantially self-contained assay means for binding an analyte suspected of being in a sample to at least one predetermined location in the first sector and optionally a second sector containing control means for conducting the assay and analyte location information, with respect to one or more analytes suspected of being in a sample, accessible to a reader, wherein the presence or absence of the analyte at said location is determinable by the reader using the control means and the location information. Depending on the nature of the assay, the disk may include fluid storage means, fluid transfer means, such as one or more capillary ducts, valves, batteries, dialyzers, columns, filters, sources of electric fields, wires or other electrical conductive means such as metallic surface deposits and the like.

The disk may have one or more sample entry ports to deliver sample fluid to the assay sector. Such ports if present are preferably sealable so that after application of the sample to the disk, the sealed disk including the sample comprises a hermetically sealed device that may be conveniently disposed of by conventional means or other disposal mechanisms for dealing with biological waste. Also, the assay sector of the disk is conveniently divided into various subsections for sample preparation and analyte separation. A waste receptacle subsection may be conveniently provided as well. The assay sector may be divided into a multiplicity of subsectors that each receives a sample. Each such subsector may analyze for one or more analytes depending on the particular application at hand.

In another aspect the invention is directed to an apparatus for conducting an assay comprising an optical disk, a disk reader and an information processor, the disk comprising a first sector having substantially self-contained assay means for localizing an analyte suspected of being in a sample to at least one, predetermined location in the

Figure 5 is a schematic representation of a chemically actuated battery useful in the present invention.

Figure 6 is a schematic representation of a structure to provide a dialysis function in the disk of this invention.

Figure 7 is a schematic representation of a column that may be included in the disk of this invention.

Figure 8 is a schematic representation of an electrically controlled valve useful in the present invention.

Figure 9 is a schematic representation of a reagent train configured in joined capillary ducts that is useful in the present invention.

Figure 10 is a schematic representation of an array of linear assay sites that are conveniently located in a flow channel in the assay sector of the disk of this invention.

Figure 11 A-C is a schematic representation of a variation of an assay element that is particularly useful for the detection of viral and bacterial particles and cells using the general methodology of site specific localization of the substance to be detected.

Figure 12 A-C is a schematic representation of a variation of the detection methodology in which opaque particles are utilized in the place of the reflective particles and bound to a reflective surface. Zig-zag lines represent oligonucleotides, but can be any recognition molecules, such antibodies. Particles are in this example plastic spheres, but can be liposomes, cells, etc.

Figure 13 is a schematic representation of an assay element of the invention illustrating the spacer molecule, with component sidearms and cleavage site, bound to a disk surface at one end and to a reporter element (gold or latex sphere) at its other end.

DETAILED DESCRIPTION OF THE INVENTION

A schematic overall representation of an integrated bio-compact disk (IBCD) is set forth in Fig. 1. The disk (Bio-Compact Disk, BCD) may be virtually of any shape and size. For most practical applications it is circular having a diameter of 10-1000 mm, most advantageously 20-200 mm and a thickness of 0.1-20 mm, most advantageously 0.5-3 mm. The disk 10 contains two sectors: an assay sector 11 and a software sector 12. A central hole 13 is provided for location in a compact disk reader. Software for controlling the assay may be on a separate disk. However, it is preferred to have the software on the disk associated with an assay for a particular analyte or analytes to minimize the opportunity for human error when performing the assay. The possible components and unit operations of the IBCD are presented in the following description.

The disk rotates typically up to 16,000 rpm in conventional CD-ROM or DVD readers. In all CD-ROM and DVD readers the speed is adjustable within certain limits (200-16,000 rpm). However, for some operations it may be advantageous to utilize rotations at differing speeds, for example 1000-10,000 rpm, and most preferably 2000-5000 rpm. For any particular assay, the controlling software dictates the rotation regimen during the analysis. This regimen, the speeds and timing, including times in which perhaps no rotation occurs to allow for incubation, electrophoresis, isoelectric focusing, etc., is controlled to deliver reagents and sample to appropriate sites on the assay sector as dictated by the assay protocols. Available rotational speeds do allow for a significant centrifugal force that may be used to move liquids. Another energy source that may be easily used in the IBCD is chemical energy. A most suitable form of chemical energy is released by a battery in the form of electrical energy. Mechanical and chemical energy allow the operation of many kinds of components. Important components of a IBCD may include one or more of the following: capillaries, containers, filters, dialysis membranes, chromatographic

sample port is preferably sealable so that at the disk is effectively sealed, except for necessary venting to allow for fluid flow, to protect from any biological hazards. By various means, e.g. centrifugal force and like means that are well known in the art, a portion of the sample is metered to a sample preparation site 15, that may contain reagents and the like in order to conduct the assay. Alternatively, or in conjunction with reagents already in the sample preparation segment, a reagent train 16 may be provided to deliver, as needed, the necessary reagents in the proper order to the sample preparation segment. Additional details of the reagent train are shown in Fig. 9. It may be necessary to separate the analyte from the sample, at least partially, and this may be done in a sample separation segment designated generally as 17. A battery 18 is provided if electrical energy is required for the separation process. Additional details of the battery are shown in Fig. 5 and described below. The resultant sample is then transferred to the assay site 19. In a preferred embodiment of the invention, the assay site contains an assay element as described in greater detail below. The analyte binds to a predetermined location on the disk if it is present in the sample, and the presence of the analyte is detected by the reader from information that identifies the particular analyte with the location at which it is bound. A waste compartment is provided to collect overflow of reagents or sample that exceeds metered amounts for use in the assay and the various compartments and fluid transfer channels are vented appropriately to allow for fluid flow throughout the surface of the assay sector.

In one embodiment of the invention, a multiplicity of assay sectors 21, 22, 23, etc. as shown in Fig. 3 may be provided, each sector connected to an individual sample inlet port 24, 25, 26 respectively. The operation of each sector is substantially as described above although different assays may be conducted at the same time in individual sectors either for a multitude of analytes or a multitude of patients. The details of a particular sector are shown in greater detail in Fig. 4, where the various

of the rotation of the lBCD, the dimensions of the capillary and the viscosity and density of the liquid. Physical properties of the liquid are dictated by the assay and the frequency of rotation is limited to a certain extent by the CD-ROM or DVD reader. Thus, the dimensions of the capillary are used to adjust the speed of the liquid transfer. The capillary ducting may be provided with "bottlenecks," i.e., restrictions in the cross-sectional areas of the capillary, to control the velocity of the liquid as necessary. Hydrophilicity and hydrophobicity may be used for the same purpose.

The exact dimensions of the capillary network and chambers may be designed by using the Navier-Stokes equation:

$$\rho v = \rho b - \nabla p + \mu \nabla^2 v$$

where ρ is the density, p is the pressure, **v** is the velocity, **b** is the body force field, μ is the viscosity and ∇ is the differential operator *del* (Mase, Continuum Mechanics, McGraw-Hill, 1970). Pressure is a scalar field, while **v** and **b** are vector fields. Commercial computer software for solving of the Navier-Stokes equation in complicated geometries is available.

Containers or compartments formed in the disk are used for sample input, to store reagents, to perform reactions and to collect waste. Their depth is about 1-2000 μm, preferably about 10-800 μm and they may have any shape possible, although circular or rectangular cross-sections are preferred. Compartments are hydrophilic, except for one end of the waste container which has an air capillary that is hydrophobic. Reaction compartments may be formed with electrodes for heating, electroconvection of electrochemical purposes. Electrodes are preferably evaporated gold films. Compartments may also have valves that are operated by electricity or chemically as described below. Storage containers may be metal coated, preferably gold coated, to prevent the penetration of the water into the plastic. Reagents may also be prepacked into cassettes, which are virtually impermeable. These cassettes

sample inlet compartment. Filters may be formed from porous plastic, glass, cross-linked cotton or cellulose, etc. These materials may be in the shape of rods or similar shapes depending on the particular use to which they are being put. Plastics, such as Teflon, may be used as films.

Since chaotropic agents are often used to denature oligonucleotides during sample preparation, it is advantageous to provide a means of dialysis in the disk to remove the salt prior to the assay being performed. As shown in Fig. 6, a dialysis unit is prepared by putting a dialysis membrane 27 on either one or both halves (top and bottom) of a compartment formed in the disk 10. Taking into account the small volumes, the buffer that is already inside the dialysis membrane is usually sufficient and typically no buffer is needed on the side of the membrane opposite the fluid layer.

A column may be prepared, such as shown in Fig. 7, by filling a compartment 28 with a desired gel, adsorbent or ion exchanger, e.g. silica gel, Sephadex, etc. (the particular material is chosen for the particular application for which it is used) and putting a filter 29 in the other end. Examples of potential uses, include separating smaller molecules from larger ones and fractionating hydrophilic and hydrophobic compounds. An ion exchange column is especially useful for the separation of nucleic acids from other biomolecules. The columns lend themselves to other uses that may be convenient or necessary for conducting any particular assay.

Fig. 8 illustrates a valve, designated generally as 30, that may be located in one end of a column or a reaction container, which has two outlet capillaries 31 and 32. In addition, there are two electrodes, 33 and 34, which are not charged initially at the position illustrated and a conductive, metallic foil 35 that is adapted to close one or the other of the capillaries depending on its position relative to each capillary. The metal foil is biased to close one of the capillaries when no current is flowing and operates to open the previously closed capillary and close the other capillary when current flows. As an example, the valve is made from a thin gold foil, which is

The assay element is preferably utilized in the assay site of the present invention. Briefly, the assay element (Fig. 13) includes a cleavable spacer 61 covalently attached at one end 60 to the disk surface 59 and at the other end 62 to a reporter element 65. The preferred embodiments of the reporter element described herein include reflective gold spheres or opaque latex spheres. Also included are two recognition elements 63a, 63b, hereafter referred to as sidearms which are covalently attached to each spacer such that the one sidearm is connected to each side of the spacer's cleavage site 64. The preferred embodiments of the sidearms described herein include oligonucleotides, antibodies and oligonucleotide-antibody conjugates. The assay elements may be used to detect the presence of an analyte and create a signal thereof through either a positive or negative recognition event (Fig. 14). A positive recognition event (Fig. 14A, C and E) occurs when an analyte 66 binds to both sidearms 63a, 63b resulting in the completion of a connective loop 67 between the two sides the spacer bisected by the cleavage site 64. A negative recognition event (Fig. 14B, D and F) occurs when analyte 66 binds to only one or neither of the sidearms 68a, 68b and consequently no loop is made connecting the two sides of the spacer. When a positive recognition event is followed by cleavage of the spacers, an unbroken connection from disk to reporter element remains intact (Fig. 14E). On the other hand, cleavage of the spacers in an assay element following a negative recognition event results in the reporter elements being disconnected from the disk (Fig. 14F). Thus, negative recognition results in loose reporter elements that are easily washed away whereas positive recognition results in the reporter elements being retained in their discrete assay sectors. In either case, the results may be observed immediately by CD-ROM or DVD reader.

Further embodiments of the invention are described herein that utilize both reflective or opaque reporter molecules, and positive and/or negative recognition events to carry out a broad range of possible assays. For example, in some assays the sidearms may be connected before a sample is added and binding of the analyte acts to

In the simplest version of the cell detection assay, the latex spheres are not connected with the IBCD before the assay, but are added after the cells are bound to the IBCD. The latex sphere suspension is added, the recognition molecules on the spheres bind to the proper cells and these cells are immobilized. These latex spheres may then be observed by reduced reflectance using the CD-ROM or DVD-reader.

Complementary Binding of Spacers

One drawback of the covalent binding of spacers is that the disk is not easily regenerated after the spacers are cleaved. If the spacers are instead connected to the substrate with complementary oligonucleotides, the disk can be regenerated after an assay is completed. The spacers or their residues are removed by heating or by using chaotropic agents. The duplexes that bind spacers are denatured and the disk can be cleaned. The disk retains the oligonucleotides that were binding old spacers. All oligonucleotides on one assay site are identical. They may be different in different assay sites, or they may be identical on the whole IBCD. New spacers having oligonucleotides complementary to those on the IBCD are added. After incubation the complementary oligonucleotides of the spacer and the IBCD hybridize. The excess spacers are washed away. In this case the oligonucleotide sidearms may be attached to the spacers before the spacers are attached to the surface. Gold spheres are then added, they are bound by the thiol groups or disulfide bridges of the spacers, and the disk is ready to be used again.

A cuvette is used for UV/Vis spectrophotometric, fluorescence or chemiluminscence assays. A cuvette in the BCD is basically a capillary that is located between a light source and a photodetector. Light can be guided by mirrors and waveguides. The number of cuvettes in the BCD varies between 0-10,000 and most advantageously between 0-50 per assay sector. The sample arrives into the most cuvettes *via* a sample preparation chamber. These chambers may contain preloaded

Centrifugal force is the main force used to transfer liquids in the IBCD. It may also be used for centrifugation, which is important when calls are separated from plasma. In this case, it is advantageous to include a filter with the sample intake container.

In the transfer of liquids, order and timing are important. In order to insure the proper sequence of arrival to a certain reaction site, liquid trains, such as illustrated in Fig. 9, may be created. In one embodiment, two main capillaries, 36 and 37, are provided that are in fluid communication with each other via connecting capillaries 38, 39 and 40. One of the main capillaries is an air channel to allow for fluid flow and typically is rendered hydrophobic. The other main channel carries the reagents in liquid form and typically is hydrophilic. The connecting capillaries and associated cavities may serve to store the reagents, generally designated 41, 42 and 43, and maintain their relative locations with respect to each other. The fluid compartment to which they are directed and their timing of delivery is controlled by their respective locations, the size of the capillaries, the density and viscosity of the fluids and the rotational speed of the disk. The liquids are separated by small air bubbles to prevent mixing, unless mixing is desired. To prevent pressure gradients air capillaries are connected upstream with all liquid capillaries. To further prevent the liquids from entering the air capillaries, these are hydrophobic.

Mixing of two solutions is performed by merging two capillaries in a Y-shaped formation. This alone provides good mixing. To guarantee more efficient mixing a capillary may have small periodic enlargements after the merge. It must be noted that rotation of the IBCD results in efficient mixing in the containers.

In dialysis the liquid is in contact with the membrane containing the buffer. The molecular weight cutoff of the membrane may be chosen to be between 300-500,000 Dalton. Because only a very thin layer of the liquid is in contact with the dialysis membrane, the dialysis is very fast. However, the ratio of the liquid to buffer

Electroconvection, electrophoresis and isoelectric focusing may each be utilized in particular applications. In electroconvection the material is transferred without trying to separate it into components. In electrophoresis the separation is the main purpose. The separation is facilitated by the use of a gel that prevents convection. Because distances are very short, the available field strength is sufficient for proper electrophoresis. For the same reason the necessary time for separation is fairly short and may be on the order of 1-5 minutes, or even less than 1 minute. Useful electroconvection may be performed in few seconds. Isoelectric focusing is basically electrophoresis in a pH gradient. A pH gradient may be created by an array of parallel capillaries, each of which contains a different buffer so that the pH changes gradually. This is demonstrated in Fig. 16. A large part of the buffer will remain in the capillaries and this will guarantee the existence of the pH gradient during the isoelectric focusing. After the focusing is completed the components can be moved along the capillaries by centrifugal force or an orthogonal electrophoresis can be performed. This method allows almost complete fractionation of human plasma proteins (Anderson, Tracy and Anderson, "The Plasma Proteins," 2nd Ed., Vol. 4, Academic Press, Inc., 1984).

A particularly advantageous configuration of an assay site is illustrated in Fig. 10. The assay element contains the spacer molecules and the reflective spheres as described previously but does so in a linear array that may be conveniently located in one or more of the capillary channels at the assay site of the disk. As has been described, analyte binds to the spacer molecules that have side arms receptive to or complementary to the analyte (as illustrated in A) and after washing the analyte that has bound is located at specific locations of the array (as illustrated in B). The presence of the bound analytes is determined by conventional address determination as with conventional compact disk readers and associated software as has been described.

Alternative embodiments of the assay element described elsewhere herein are useful for the detection of viral and bacterial particles, cells and other particles that are larger than the oligonucleotides, antibodies, antigens and the like that have been described previously. Viruses are typically nearly spherical particles having a diameter less than 0.5 μm. Bacteria are commonly either spherical or rod shaped. Their largest dimension is less than 2 μm excluding flagella and other similar external fibers. These pathogens are smaller or about the same size as the gold spheres used to detect them, and their interaction with two sidearms of the spacer may be limited. For this reason these sidearms are connected with the surface of the IBCD and the gold sphere instead of with the spacer as illustrated in Fig. 11. The gold sphere is attached to a spacer molecule 45 at one end of the spacer molecule and the other end of the spacer is attached to the surface of the substrate 46. The spacer molecule is provided with a typical cleavage site 47, for example a siloxane moiety, as has been previously described. In contrast to prior described embodiments where the side-arms are attached to the spacer molecule between the substrate and the cleavage site and the gold sphere and the cleavage site, side arms are attached to the gold sphere and to the surface of the substrate. For illustration purposes, in Fig. 11 oligonucleotides 48 and 49 are attached to the surface of the substrate and oligonucleotides 50 and 51 are attached to the surface of the gold sphere. Then complementary oligonucleotides are conjugated with members of a specific binding pair, designated as 52, 53, 54, and 55 are attached to the oligonucleotides on the substrate and the gold sphere as illustrated. This gives much more space for the cells to bind with the antibodies or other recognition molecules.

The spacers each still have at least one cleavage site. They are, in all respects identical to those described previously except that they have no attached sidearm molecules. When the cell for example arrives at the assay site, if it contains moieties that form specific binding pairs with their respective complementary members, a connective loop is formed between the gold sphere and the substrate. When the

recognition molecules completes a connective loop that binds the gold sphere to the surface of the IBCD. After cleaving the spacer, the gold sphere is retained and detected by the CD-ROM or DVD reader.

A multiplicity of different recognition molecules in the same assay site may be used. The advantage of this approach is that all known mutants of a certain pathogen species may be detected on one assay site. The various mutants also may be characterized on different assay sites containing specific recognition molecules.

The IBCD is a universal analyzer. It is easy to use and in its most advanced form it contains all reagents and only the sample is added. It can be used in clinical laboratories, hospitals, doctors' offices, and in the home. In home use the information can be loaded into a doctor's office *via* the internet. The IBCD can be designed so that the genetic signature of each patient is measured every time. About 35 polymorphism points are enough to give every person a unique "bar-code". This eliminates possible mistakes due to mixing of tubes or labels. Assays that can be performed include, but are not limited to immunoassays, DNA testing, cell counting and cell shape measurement, detection of cancerous cells in tissue samples, blood chemistry and electrolyte analysis. Other applications include mass screening of drug candidates, food and environmental safety analysis, and monitoring pathogens and toxins in a battlefield.

EXAMPLE 3

Turbidimetric assay of lipase activity.

The reagent cavity contains 15 μL of stabilized triolein (250 μM) emulsion that contains sodium deoxycholate (30 mM) and $CaCl_2$ (100 μM) at pH 9.0 in TRIS buffer (25 mM). The sample preparation chamber contains lyophilized porcine colipase (0.5 μg). Two microliters of serum is taken into the sample preparation chamber (using apparatus as shown in Fig. 17) together with stabilized triolein and

What is Claimed Is:

1. An optical disk, adapted to be read by an optical reader, comprising a first sector having a substantially self-contained assay means for binding or reacting an analyte suspected of being in a sample to at least one, predetermined location in the first sector and optionally a second sector containing a control means for conducting the assay and analyte location information with respect to one or more analytes suspected of being in a sample, accessible to a reader, and wherein the presence or absence of the analyte at said location is determinable by the reader using the control means and the location information.

2. The optical disk of Claim 1 which includes a sealable sample entry port in fluid communication with the assay means.

3. An apparatus for conducting an assay comprising an optical disk, a disk reader and an information processor, wherein the disk comprises a first sector having a substantially self-contained assay means for binding an analyte suspected of being in a sample to at least one, predetermined location in the first sector and optionally a second sector containing control information for conducting the assay and analyte location information with respect to one or more analytes suspected of being in the sample, accessible to the reader and processable by the information processor, wherein the disk is adapted to be read by the reader and the information processor is adapted to determine the presence or absence of the analyte at said location using the control information and the location information.

4. The apparatus of Claim 3 wherein the reader is a CD-ROM or a DVD reader and wherein the reader is adapted to be coupled to an information processor.

5. The apparatus of Claim 4 wherein the information processor is a personal computer.

the cleavage site for binding to a first part of the analyte and a second moiety between the second end of the spacer molecule and the cleavage site for binding to a second part of the analyte.

15. An assay component, adapted to be read by a CD-ROM or a DVD reader comprising an optical disk and a substantially self-contained assay means in the disk for binding an analyte suspected of being in a sample to at least one, predetermined location on the disk and means at said location for enabling detection of the absence or presence of the analyte by the CD-ROM or the DVD reader.

16. An optical disk, adapted to be read by a CD-ROM or a DVD reader comprising a substantially self-contained assay means for localizing an analyte suspected of being in a sample to at least one, predetermined location on the disk and a means at said location for detecting the absence or presence of the analyte by the CD-ROM or the DVD reader.

FIG. 2B

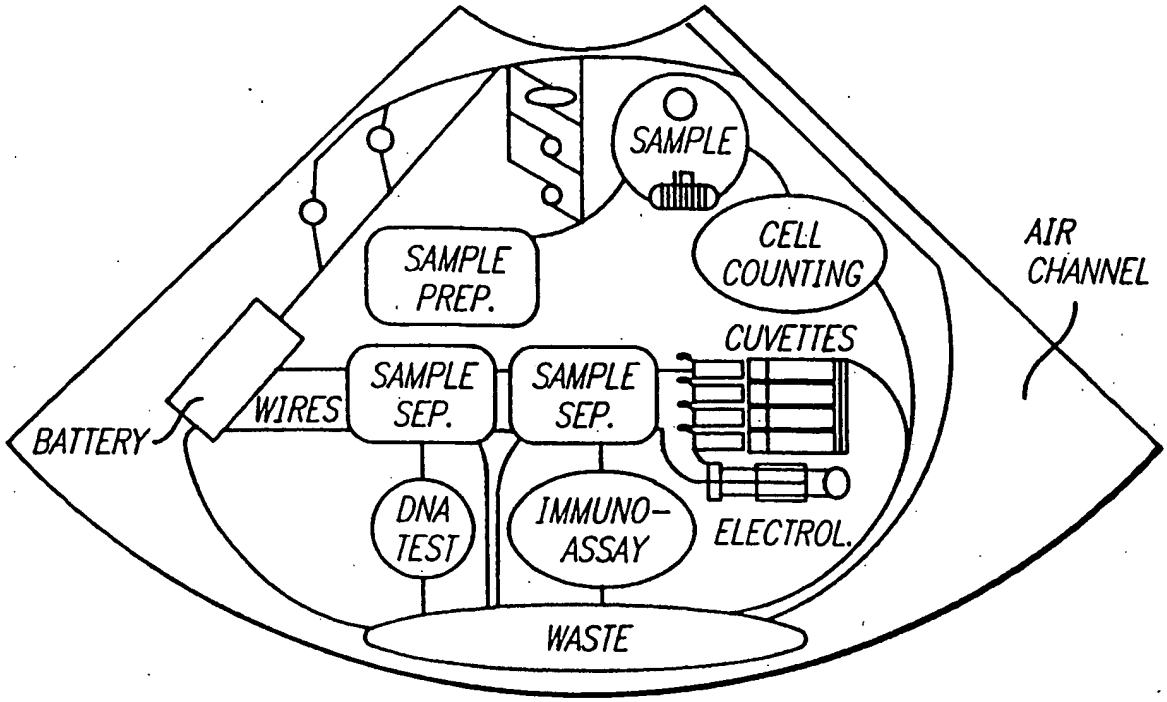

SAMPLE
CELL COUNTING
AIR CHANNEL
SAMPLE PREP.
CUVETTES
BATTERY
WIRES
SAMPLE SEP.
SAMPLE SEP.
DNA TEST
IMMUNO-ASSAY
ELECTROL.
WASTE

FIG. 3

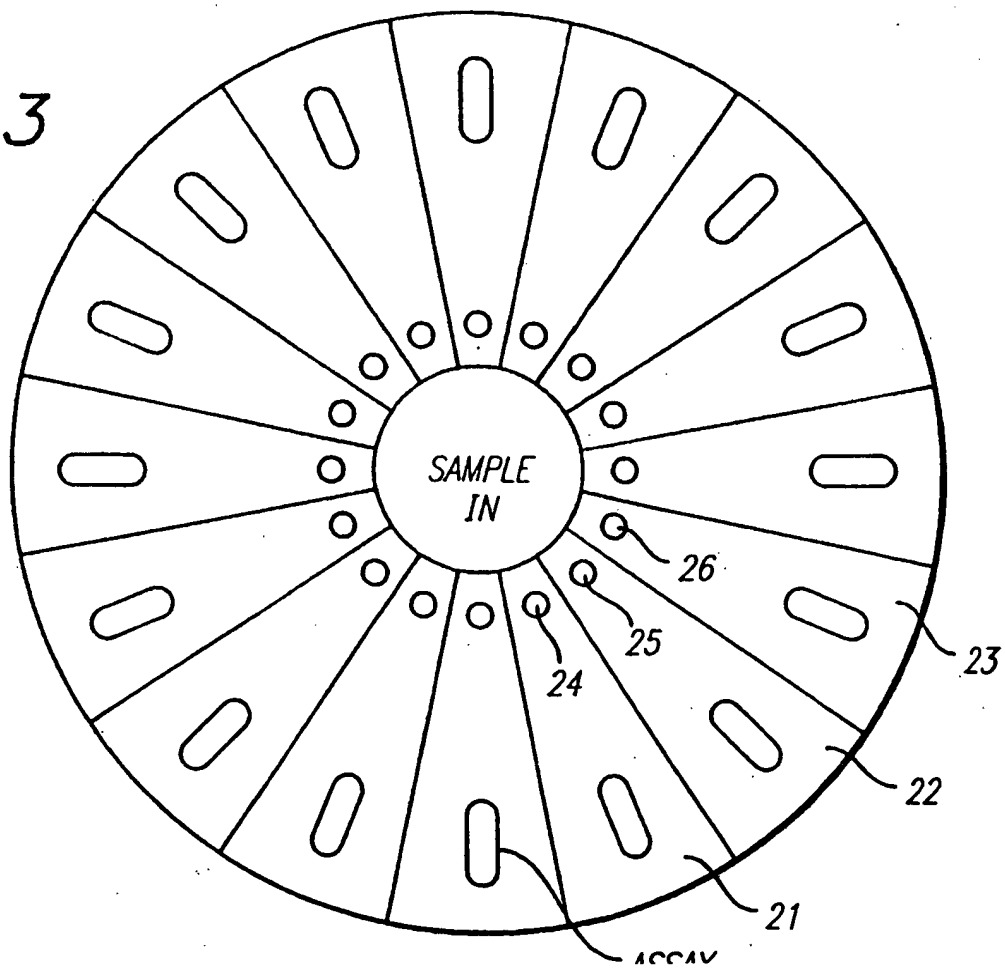

SAMPLE IN
26
25
24
23
22
21

FIG. 6

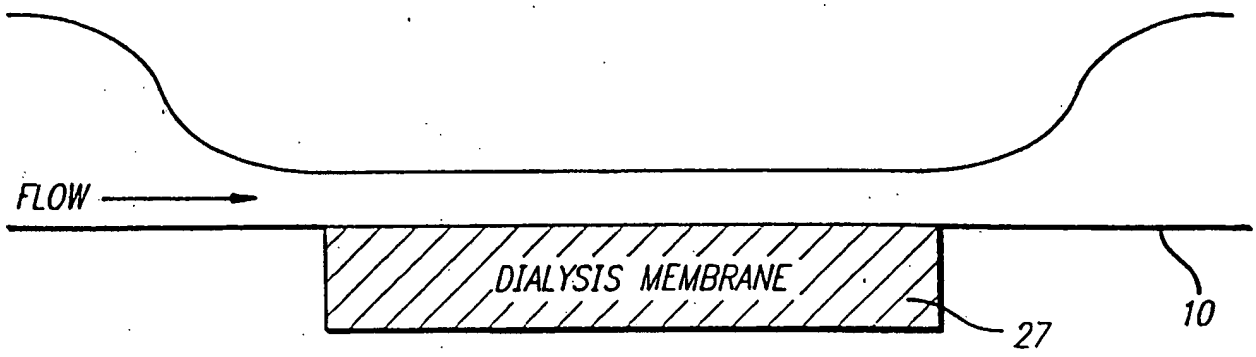
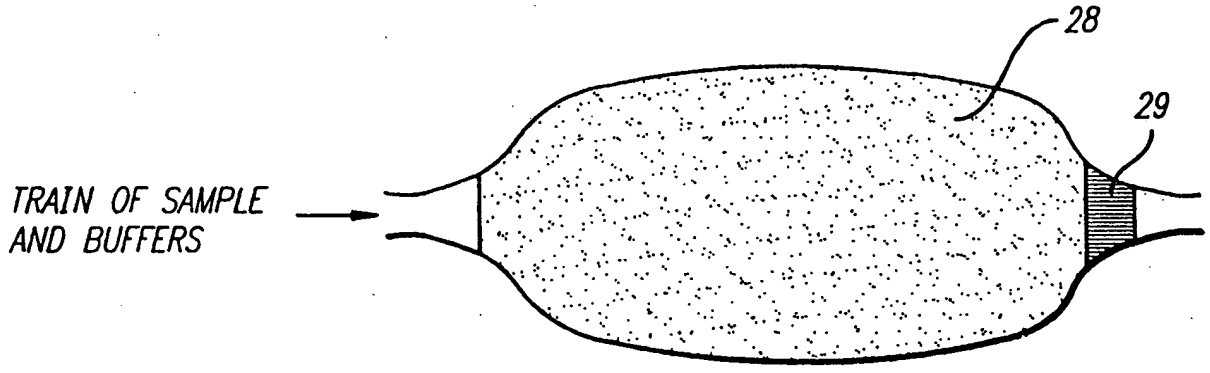

FLOW
DIALYSIS MEMBRANE
27
10

FIG. 7


28
29
TRAIN OF SAMPLE
AND BUFFERS

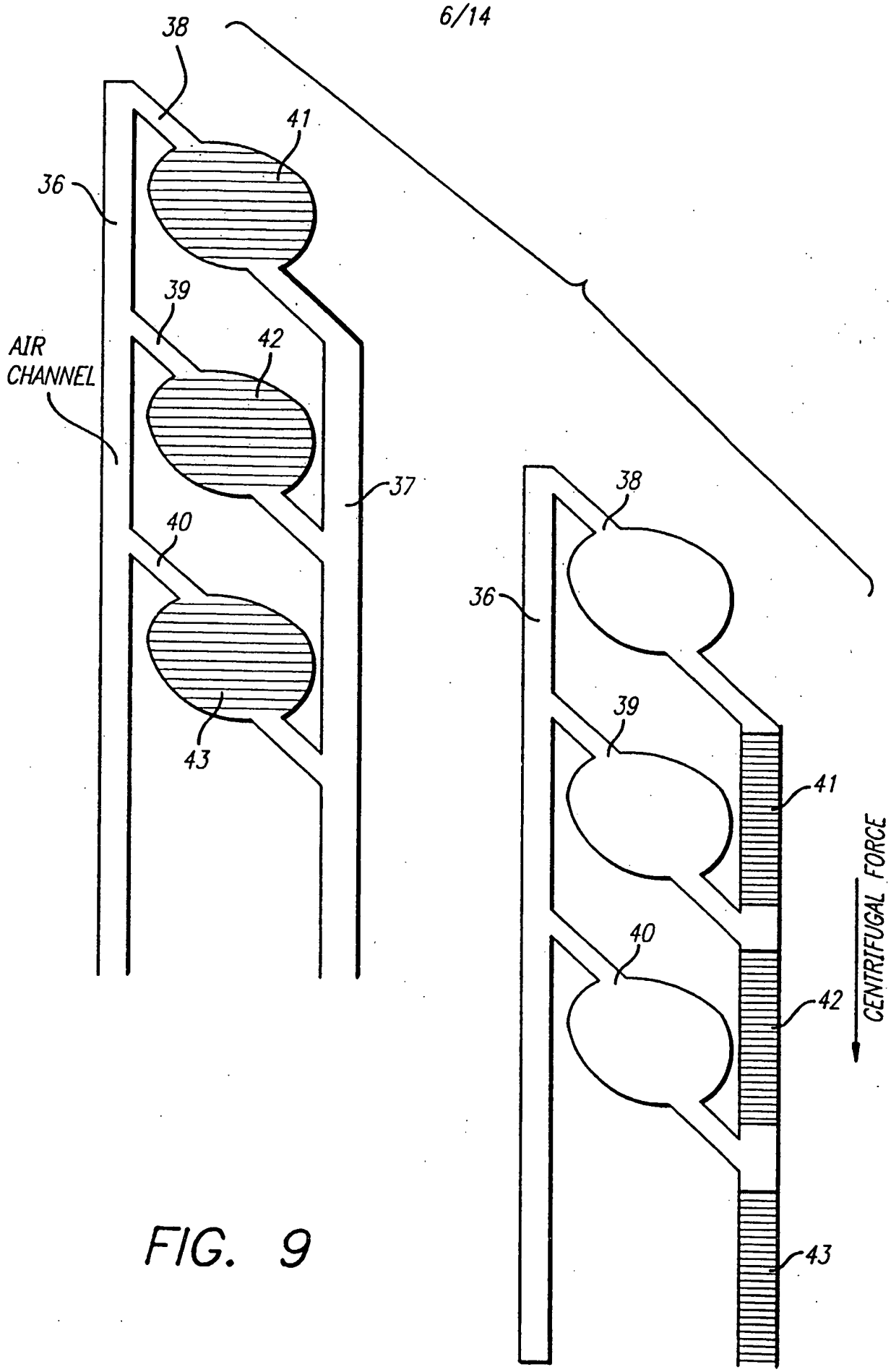

38
41
36
39
AIR
CHANNEL
42
37
40
43
38
36
39
41
CENTRIFUGAL FORCE
40
42
43

FIG. 9

FIG. 11A

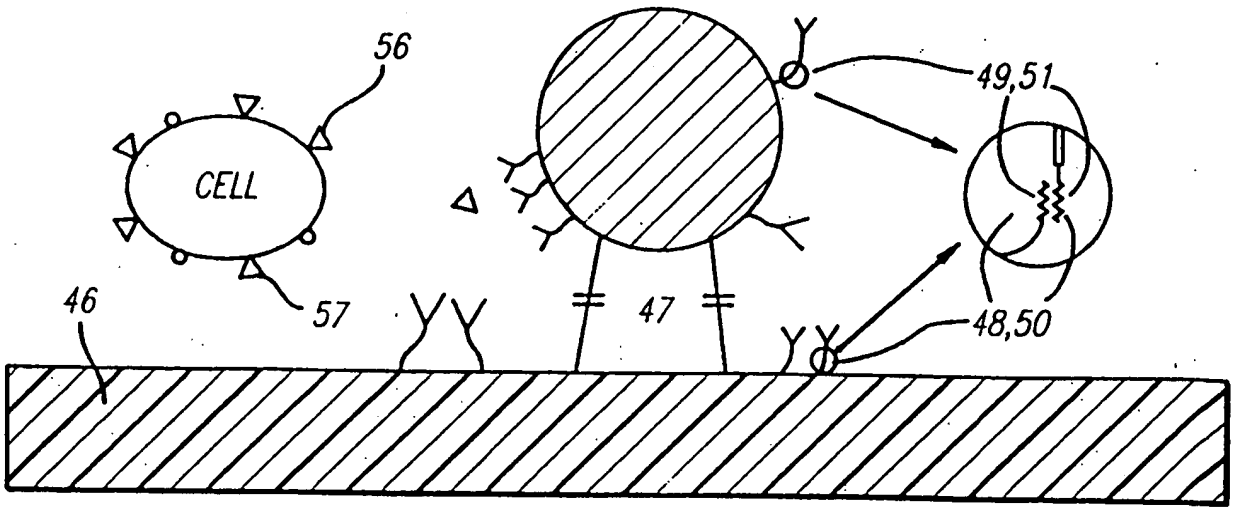


FIG. 11B

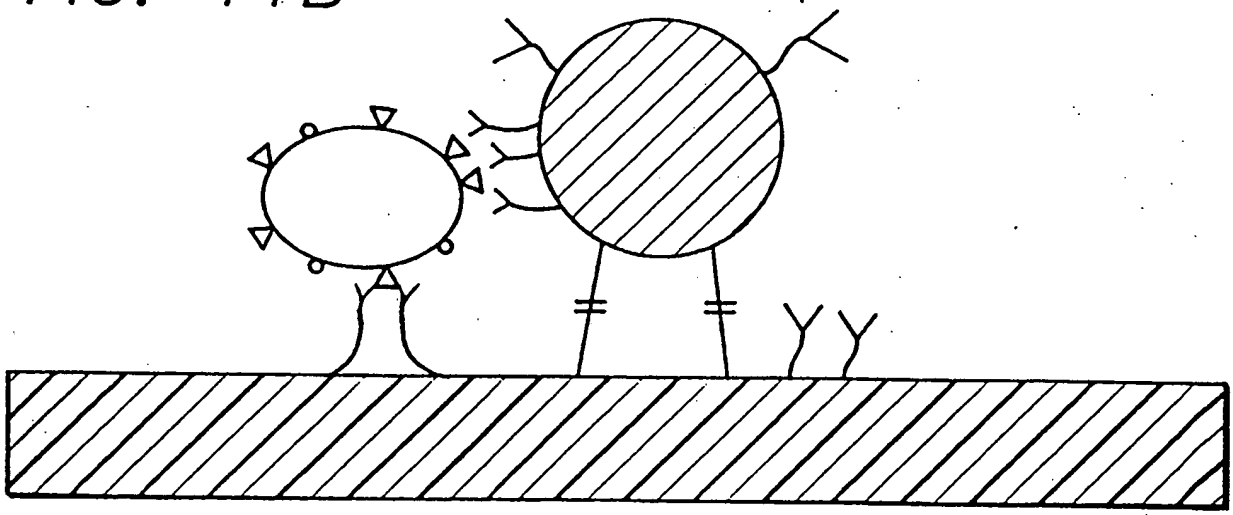


FIG. 11C

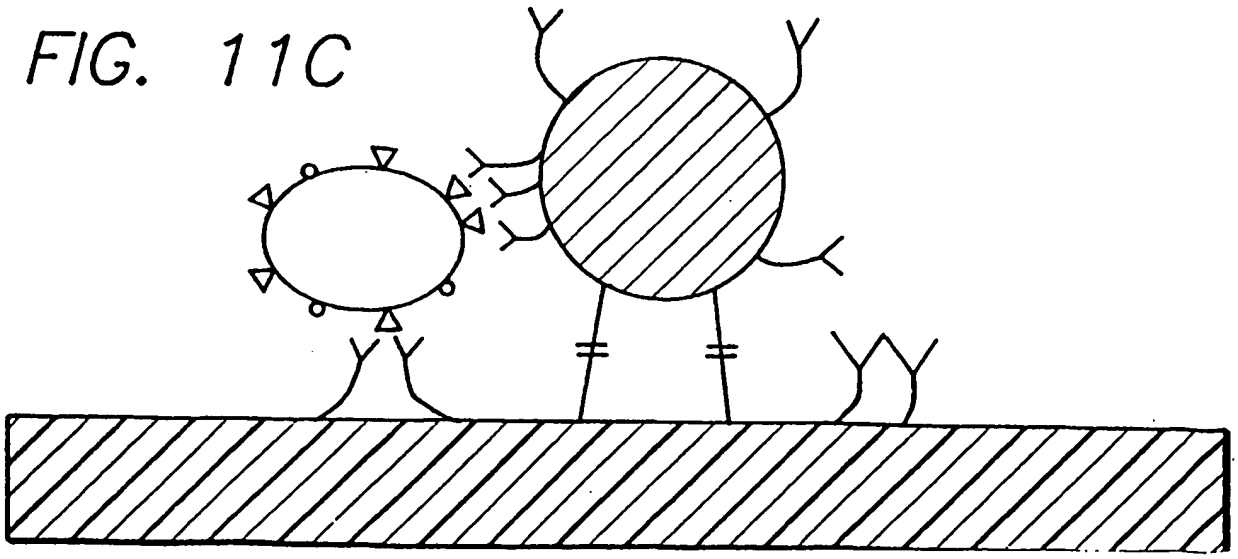


FIG. 13

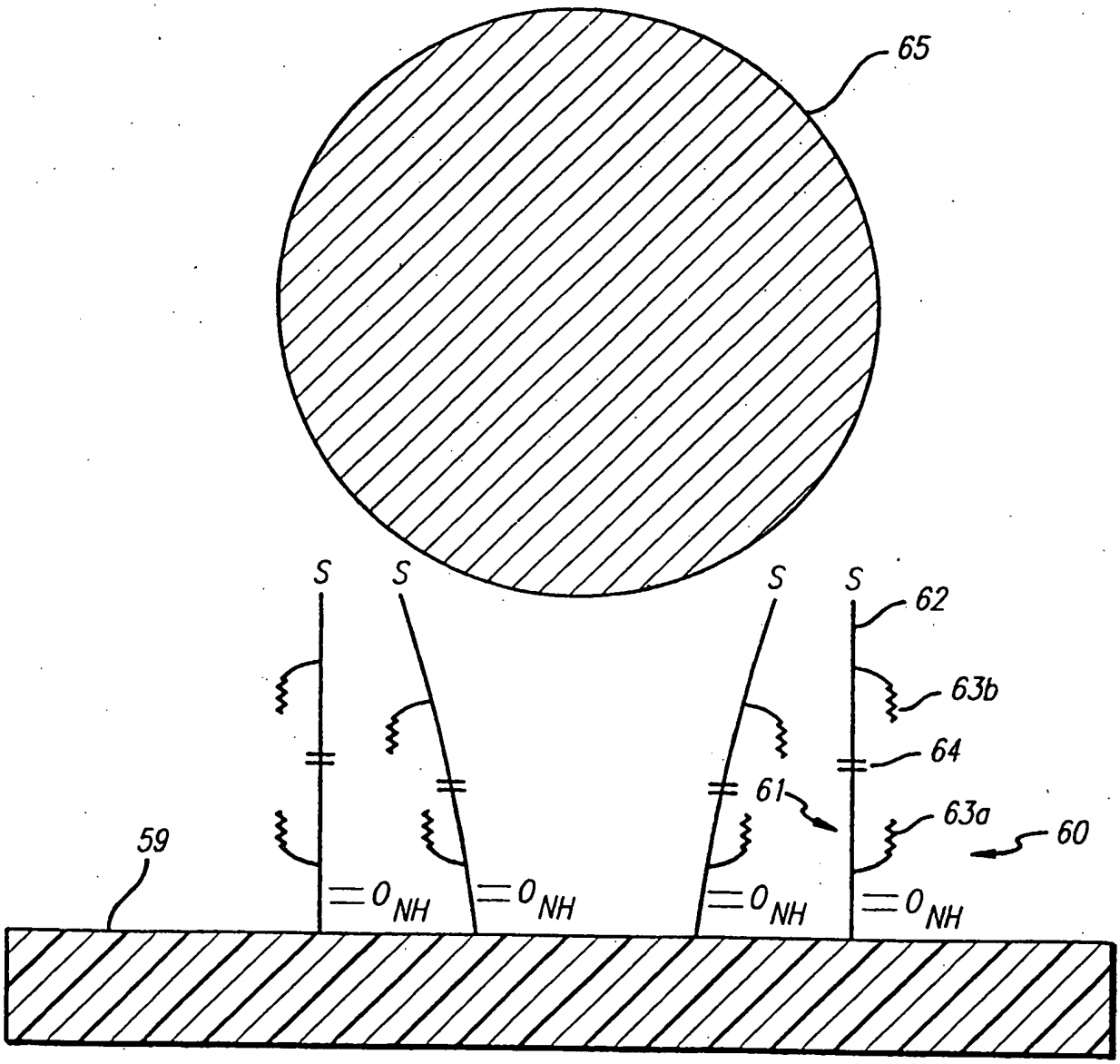


FIG. 15A

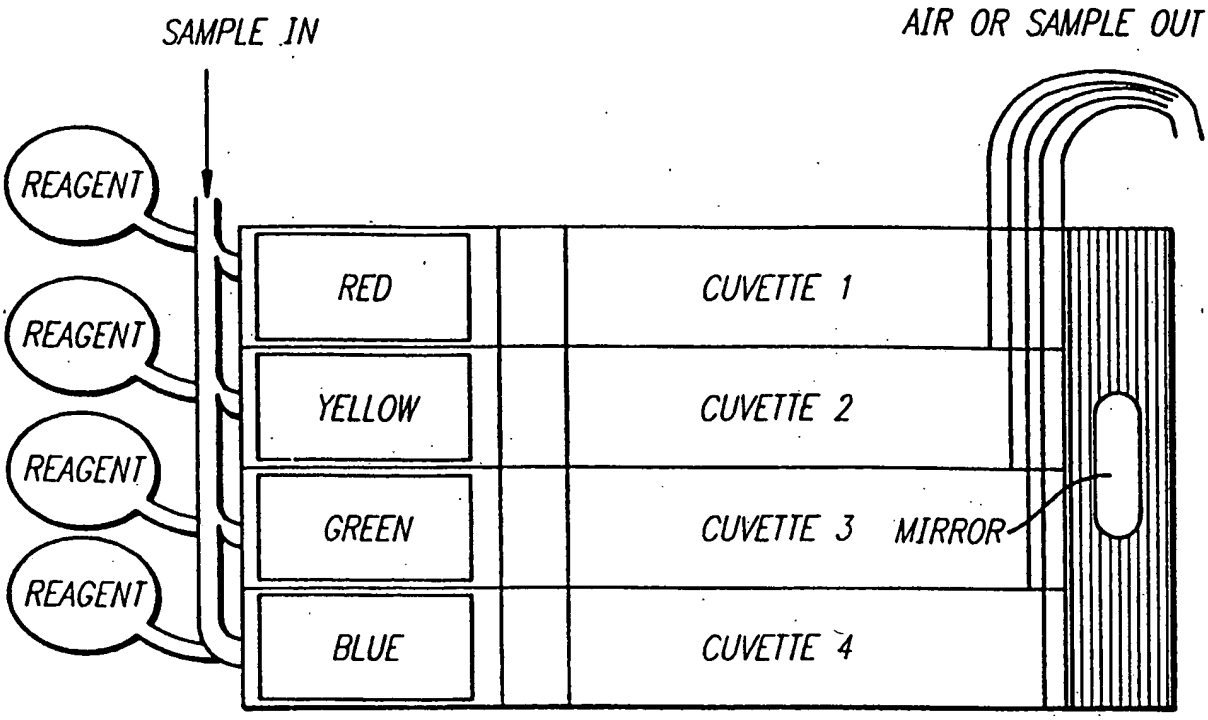
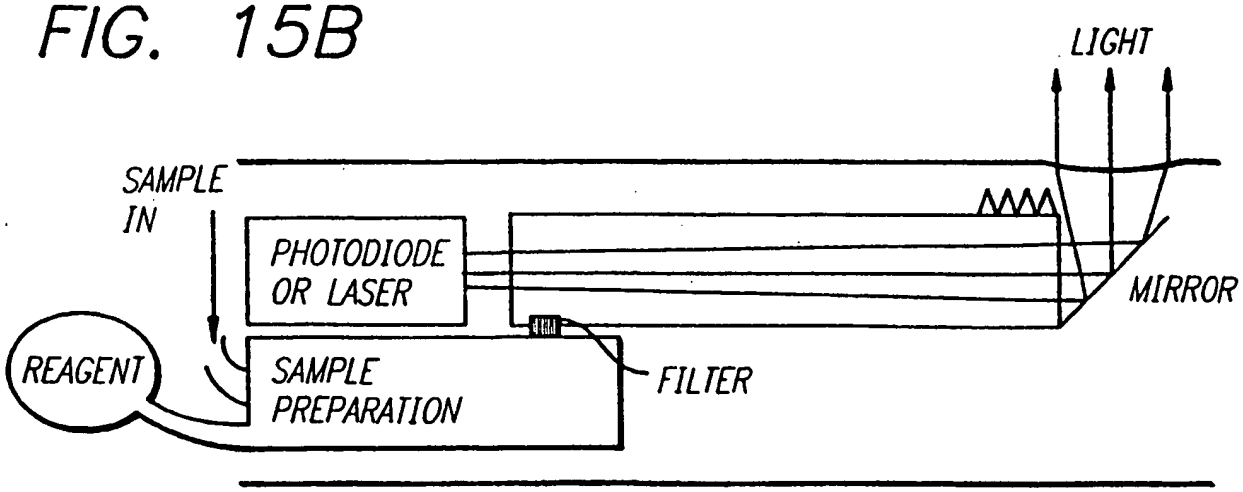
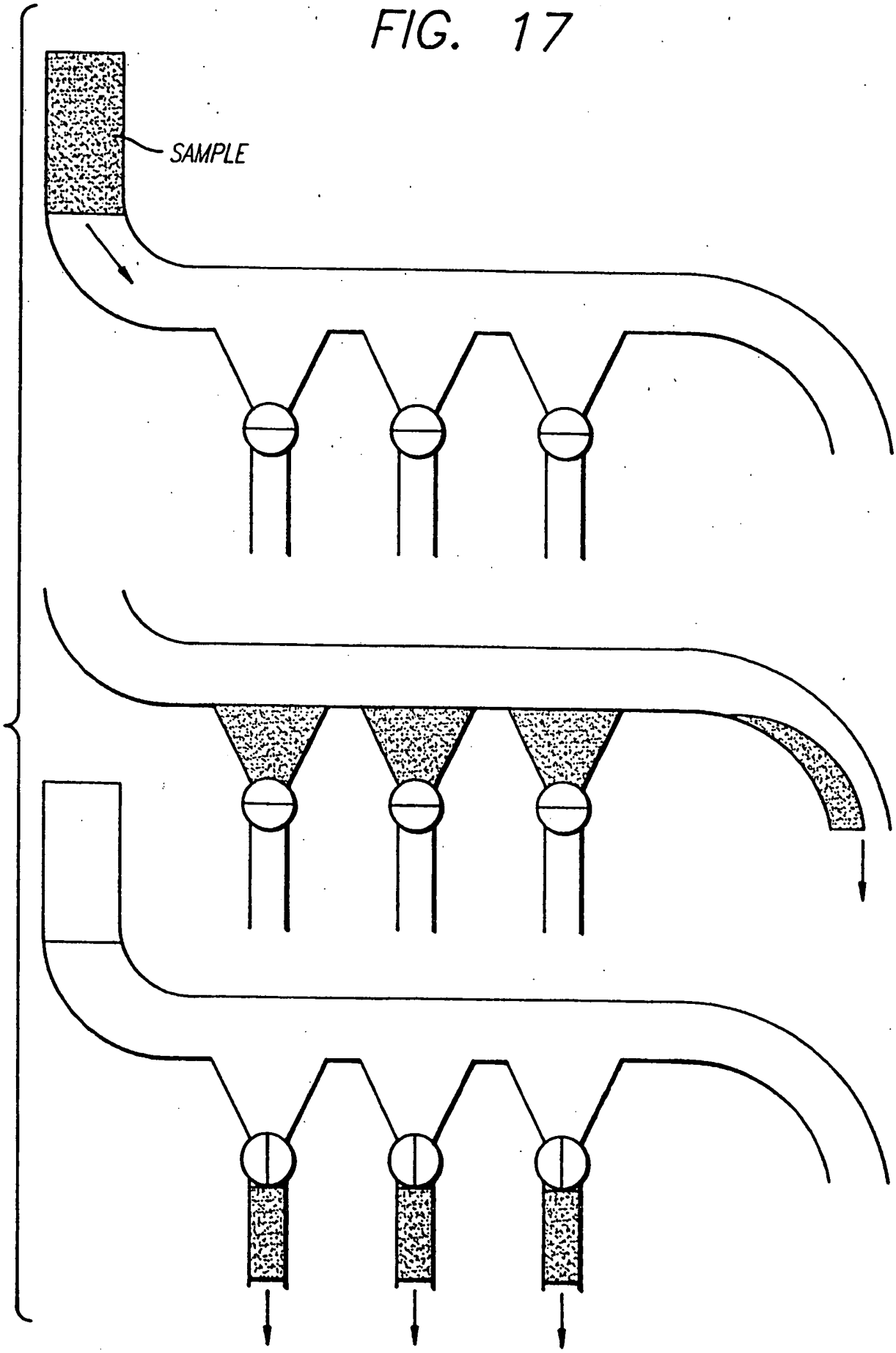


FIG. 15B



CUVETTE ASSEMBLY

FIG. 17



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(74) Agent: HALLUIN, Albert, P.; Howrey & Simon, 1299 Pennsylvania Avenue, N.W., Box 34, Washington, DC 20004-2402 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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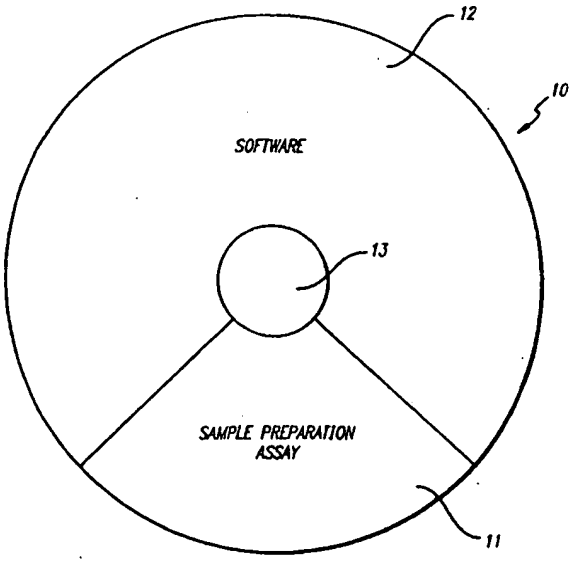
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
28 January 1999 (28.01.99)

(54) Title: LABORATORY IN A DISK



(57) Abstract

An apparatus is described that includes an optical disk, adapted to be read by an optical reader, comprising a first sector having substantially self-contained assay means for localizing an analyte suspected of being in a sample to at least one, predetermined location in the first sector and a second sector containing control means for conducting the assay and analyte location information, with respect to one or more analytes suspected of being in a sample, accessible to the reader, wherein the presence or absence of the analyte at said location is determinable by the reader using the control means and the location information. Depending on the nature of the assay, the disk will include fluid storage means, fluid transfer means, such as one or more capillary ducts, valves, batteries, dialyzers, columns, filters, sources of electric fields, wires or other electrical conductive means such as metallic surface deposits and the like.

INTERNATIONAL SEARCH REPORT

Im ational Application No
PCT/US 98/04377

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N35/02 G01N33/487 G01N33/50 G01N21/64 G01N33/483 //C12Q1/68

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 96 09548 A (THE UNIVERSITY COURT OF THE UNIVERSITY OF GLASGOW) 28 March 1996 see page 10, line 16 - page 24, line 10; figures 1-7	1,3-5, 12,15,16 6,7,10, 11,13
Y	EP 0 417 305 A (IDEMITSU PETROCHEMICAL CO. LTD.) 20 March 1991 see column 5, line 35 - column 15, line 13; figures 1-12	6,7,11, 13
Y	CAROL T. SCHEMBRI, ET AL.: "Portable Simultaneous Multiple Analyte Whole-Blood Analyzer for Point-of-Care Testing" CLINICAL CHEMISTRY., vol. 38, no. 9, September 1992, pages 1665-1670, XP000319980 WINSTON US see the whole document	10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 September 1998	07. 12. 98

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Authorized officer
Osborne, H

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 04377

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see attached sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ational Application No
PCT/US 98/04377

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